258. *Synthetic Neuromuscular Blocking Agents. Part I. Heterocyclic Decamethylenebis(quaternary Ammonium Salts).*

By E. P. Taylor.

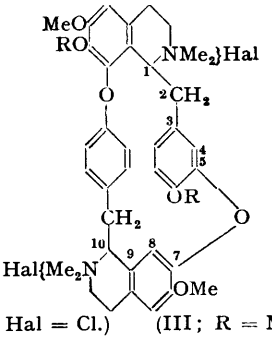
A series of heterocyclic decamethylenebis(quaternary ammonium salts) has been prepared, some of which possess greater curarising activity in rabbits than does (+)-tubocurarine chloride.

It has long been known that the presence of a quaternary nitrogen atom in a molecule is associated with curarising activity. In 1948, Barlow and Ing (*Nature*, 1948, **161**, 718 : *Brit. J. Pharmacol.*, 1948, **3**, 298), and Paton and Zaimis (*Nature*, 1948, **161**, 718), independently investigated the pharmacological activities of a series of polymethylene-αω-bistrimethylammonium salts. Both pairs of workers found the maximum neuromuscular blocking activity to be shown by decamethylenebis(trimethylammonium iodide), now known as decamethonium iodide or C. 10.

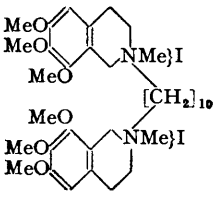
Since the molecule of (+)-tubocurarine chloride (I) also possesses two quaternary nitrogen atoms separated by a chain of ten atoms, it was decided to investigate the effect of maintaining the chain-length at ten, but altering the nature of the terminal quaternary nitrogen groups.

The relation between " curariform " activity and chemical structure has been fully reviewed by Craig (*Chem. Reviews*, 1948, **42**, 285) who states, *inter alia*, that " in general, all of the really effective curare-like compounds have the nitrogen present in a saturated ring," and " the methoxyl group enhances curare action."

The pharmacological properties of the present series of compounds were determined by Dr. H. O. J. Collier, and most have already been briefly reported (Collier and Taylor, *Nature*, 1949, **164**, 491; Taylor and Collier, *ibid.*, 1950, **165**, 602).



(I; R = H, Hal = Cl.) (III; R = Me. Hal = I.)



(II.)

Neostigmine antagonises all of the six compounds of this series which have been examined for this effect in the rabbit. Furthermore, the two most active compounds have been administered to chicks, producing the flaccid paralysis typical of true curariform activity (Buttle and Zaimis, *J. Pharm. Pharmacol.*, 1949, **1**, 991). It can therefore be concluded that the paralysing action of compounds of this type is curariform. The curarising activites of our compounds in rabbits and mice are indicated in Table I. The last three substances

TABLE I.

Paralysing activity of decamethylenebis(quaternary ammonium salts).

(All values in mg. per kg. of body weight.)

Nature of X in $I^- {}^+\{X\cdot[CH_2]_{10}\cdot X\}^+ I^-$.	MED (rabbit).	ED. 50 (mouse).
Quinolinium	4·5	0·9
1 : 2 : 3 : 4-Tetrahydro-1-methylquinolinium	0·75	0·9
cis-Decahydro-1-methylquinolinium	0·12	convulsant
trans- ,, ,,	0·1	0·75
trans-1-Ethyldecahydroquinolinium	0·4	—
6-Methoxyquinolinium	*ca.* 4·0	1·3
1 : 2 : 3 : 4-Tetrahydro-6-methoxy-1-methylquinolinium	0·2	1·0
8-Methoxyquinolinium	0·2	0·8
1 : 2 : 3 : 4-Tetrahydro-8-methoxy-1-methylquinolinium	0·1	0·6
8-Ethoxyquinolinium	>0·3	—
8-Ethoxy-1 : 2 : 3 : 4-tetrahydro-1-methylquinolinium	*ca.* 0·1	—
6 : 7-Dimethoxyquinolinium	0·15	0·4
1 : 2 : 3 : 4-Tetrahydro-6 : 7-dimethoxy-1-methylquinolinium	0·08	0·65
*iso*Quinolinium *	*ca.* 4·0	3·6
1 : 2 : 3 : 4-Tetrahydro-2-methyl*iso*quinolinium	1·5	1·9
cis-Decahydro-2-methyl*iso*quinolinium	<0·5	0·7
1 : 2 : 3 : 4-Tetrahydro-6-methoxy-2-methyl*iso*quinolinium	0·2	0·9
6 : 7-Dimethoxy*iso*quinolinium	>1·0	1·8
1 : 2 : 3 : 4-Tetrahydro-6 : 7-dimethoxy-2-methyl*iso*quinolinium	0·05	0·35
1 : 2 : 3 : 4-Tetrahydro-6 : 7 : 8-trimethoxy-2-methyl*iso*quinolinium	0·02	0·3
1 : 2 : 3 : 4-Tetrahydro-2-methyl-6 : 7-methylenedioxy*iso*quinolinium	0·25	1·2
1 : 2 : 3 : 4-Tetrahydro-2-methyl-6 : 7-methylenedioxy-8-methoxy*iso*quinolinium	0·12	0·85
4-Methylmorpholinium	—	No paralysis
Pyridinium *	—	1·9
1-Methylpiperidinium	—	2·0
3-Bromopyridinium	8·0	0·5
3-Methoxypyridinium	—	No paralysis at 5·0
1-Methylpyrrolidinium	—	1·25 to 1·5
Decamethonium iodide (C. 10)	0·15	0·6
(+)-Tubocurarine chloride	0·1	0·1
(+)-*OO*-Dimethyltubocurarine iodide	0·01	0·12

* Bromide.

are inserted for comparison only. The full pharmacological results will be reported elsewhere by Dr. H. O. J. Collier. It will be observed, however, that, in accordance with the requirements quoted by Craig (*loc. cit.*), reduction of the heterocyclic nucleus, or introduction of methoxyl groups, enhances the curarising activity in the rabbit. The most active of the present series of compounds, decamethylenebis-(1 : 2 : 3 : 4-tetrahydro-6 : 7 : 8-trimethoxy-2-methyl*iso*-quinolinium iodide) (II) has each nitrogen atom in a saturated ring and three methoxyl groups in each heterocyclic nucleus. Moreover, it exhibits a close chemical resemblance to (+)-*OO*-dimethyltubocurarine iodide (III). In the rabbit, it is approximately seven times as active as decamethonium iodide, and approximately five times as active as (+)-tubocurarine chloride, and, in this mammal, is one of the most active, purely synthetic, neuromuscular blocking agents yet prepared. It is awaiting clinical trials.

The bisquaternary salts were prepared by two general methods: (i) An excess (usually 50%) of the appropriate tertiary amine was refluxed with a decamethylene dihalide in a neutral solvent (for example, benzene) for, in general, 24—48 hours. The speed and degree of completion of the reaction could be approximately gauged by the rate of precipitation of the required salt. (ii) A 200% excess of an appropriate secondary amine refluxed with a decamethylene dihalide in benzene solution yielded the corresponding bistertiary amine (again, the speed of reaction could be judged by the rate of separation of the hydrohalide of the secondary amine). Treatment of the purified bistertiary amine with an ethereal or benzene solution of an alkyl halide yielded the required bis(quaternary ammonium salt).

However, when 1 : 2 : 3 : 4-tetrahydro-6 : 7-dimethoxy-1-methylquinoline was refluxed with a benzene solution of decamethylene di-iodide, a very slow reaction occurred, and the resultant quaternary compound, obtained only in a very poor yield, proved to be the methiodide of the original base. In order to obtain decamethylenebis-(1 : 2 : 3 : 4-tetrahydro-6 : 7-dimethoxy-1-methylquinolinium iodide), it was necessary to treat 1 : 2 : 3 : 4-tetrahydro-6 : 7-dimethoxyquinoline first with decamethylene di-iodide, and then with methyl iodide.

Neither 2-methoxypyridine nor 8-methylthioquinoline reacted with decamethylene di-iodide during one month's refluxing. These failures may be due to steric hindrance, since 8-methoxyquinoline reacted with decamethylene di-iodide much more slowly than did the 6-methoxy-compound. Moreover, 8-ethoxyquinoline and decamethylene di-iodide in benzene slowly gave material of vague melting point, probably the monoquaternary compound, 8-ethoxy-1-10′-iododecylquinolinium iodide; if this compound was kept in solution by using alcohol as the solvent instead of benzene, and a further excess of 8-ethoxyquinoline added, the required bisquaternary derivative could be prepared.

Reaction between 6 : 7 : 8-trimethoxyquinoline and decamethylene di-iodide was exceedingly slow, even when alcohol was used. The product, obtained only in very small yield, is as yet unidentified.

6 : 7 : 8-Triethoxy-1 : 2 : 3 : 4-tetrahydro-2-methyl*iso*quinoline reacted very little with decamethylene di-iodide in benzene; in xylene a black oil separated which yielded a very small quantity of 6 : 7 : 8-triethoxy-3 : 4-dihydro-2-methyl*iso*quinolinium iodide.

Experimental.

(Analyses are by Drs. Weiler and Strauss, Oxford. All m. p.s and b. p.s are uncorrected.)

I. *Preparation of Simple Heterocyclic Secondary and Tertiary Amines.*—Commercial products, when available, were purified by distillation, recrystallisation, or recrystallisation of derivatives such as the picrates.

Other amines were prepared by the methods described in the literature or as indicated below. For reduction of quinoline and *iso*quinoline derivatives to the tetrahydro-derivatives, sodium and boiling alcohol gave better results than tin and hydrochloric acid (cf. Bamberger and Dieckmann, *Ber.*, 1893, **26**, 1208). The conversion of *N*-alkyl-quinolinium and -*iso*quinolinium halides into the corresponding *N*-alkyltetrahydro-quinolines and -*iso*quinolines was effected by zinc dust and hydrochloric acid, followed by sodium and alcohol, to avoid the possibility of formation of *N*-alkyl dihydro-derivatives.

Quinoline Derivatives.—*cis*- and *trans*-Decahydroquinoline: commercial decahydroquinoline was separated into the *cis*- and *trans*-forms as described by Bailey and McElvain (*J. Amer. Chem. Soc.*, 1930, **52**, 4015).

1 : 2 : 3 : 4-Tetrahydro-6- and -8-methoxy-, and 8-ethoxy-1 : 2 : 3 : 4-tetrahydro-quinoline were obtained by reduction of the corresponding 6- or 8-substituted quinoline derivatives.

6 : 7-Dimethoxyquinoline was prepared by the Skraup reaction from 3 : 4-dimethoxyaniline (Found: C, 69·9; H, 5·8; N, 7·2. Calc. for $C_{11}H_{11}O_2N$: C, 69·8; H, 5·9; N, 7·4%). It has been described by Frisch and Bogert (*J. Org. Chem.*, 1943, **8**, 334) and by Sugasawa, Kakemi, and Tsuda (*Proc. Imp. Acad.*,

Tokyo, 1938, **14**, 67 : *J. Pharm. Soc., Japan*, 1938, **58**, 402), whose data are compared with ours in the following table.

	M. p. or b. p.		
	This paper.	F. and B.	S. *et al.*
Base	33—35°	—	—
	190—191°/11 mm.	164°/2·3 mm.	—
Hydrochloride	233—234 *	222	232° *
Picrate	256	257	251—252 *
Methiodide	271 †	242 *	—
	261 ‡	—	—

* With decomp. † Rapid heating. ‡ Slow heating.

1 : 2 : 3 : 4-Tetrahydro-6 : 7-dimethoxyquinoline, prepared by reduction of the quinoline derivative, crystallised from ether–light petroleum (b. p. 40—60°) as needles, m. p. 43—45°, b. p. 189—191°/9 mm. (Levitz and Bogert, *J. Org. Chem.*, 1945, **10**, 345, give m. p. 45—45·5°). The hydrochloride crystallised from alcohol as needles, m. p. 192—193° (Sugasawa, Kakemi and Tsuda, *loc. cit.*, give m. p. 196°).

1 : 2 : 3 : 4-Tetrahydro-6 : 7-dimethoxy-1-methylquinoline, obtained by reduction of 6 : 7-dimethoxyquinoline methiodide, formed needles, m. p. 45°, b. p. 174—176°/10 mm., from light petroleum (b. p. 40—60°) (Found : C, 69·6; H, 8·2; N, 6·8. Calc. for $C_{12}H_{17}O_2N$: C, 69·6; H, 8·3; N, 6·8%); its methiodide, prisms (from alcohol), had m. p. 216—217° (Levitz and Bogert, *loc. cit.*, record the base as an oil, b. p. 135—136°/1 mm., and the methiodide as having m. p. 216·5—217·5°).

6 : 7 : 8-*Trimethoxyquinoline*. 2 : 3 : 4-Trimethoxyaniline had b. p. 95—97°/0·1 mm., 154°/13 mm., and its hydrochloride had m. p. 200° (decomp.) (contrast Lions, *J. Proc. Roy. Soc., N.S.W.*, 1929, **63**, 159; Graebe and Suter, *Annalen*, 1905, **340**, 227; Hupe and Schramme, *Z. physiol. Chem.*, 1928, **177**, 317).

The Skraup reaction with 2 : 3 : 4-trimethoxyaniline in nitrobenzene proceeded with almost explosive violence, and it was advisable to use arsenic pentoxide as described by Mietzsch and Klös (U.S.P. 1,790,066) for 6 : 8-dimethoxyquinoline. The resulting 6 : 7 : 8-trimethoxyquinoline melted at 80°, and its picrate at 181°. The *methiodide* separated from ether–alcohol as pale yellow needles, m. p. 139—140° (decomp.) (Found : C, 42·9; H, 4·6; N, 4·0; I, 34·9. $C_{13}H_{16}O_3NI$ requires C, 43·2; H, 4·5; N, 3·9; I, 35·2%).

1 : 2 : 3 : 4-*Tetrahydro*-6 : 7 : 8-*trimethoxyquinoline*, prepared by reduction of the quinoline derivative, had b. p. 139—141°/0·6 mm. (Found : C, 65·0; H, 7·7; N, 6·4. $C_{12}H_{17}O_3N$ requires C, 64·6; H, 7·7; N, 6·3%). The *hydrochloride* crystallised from ether–alcohol as needles, m. p. 206—208° (decomp.) (Found : C, 55·7; H, 7·0; N, 5·2; Cl, 13·5. $C_{12}H_{18}O_3NCl$ requires C, 55·5; H, 7·0; N, 5·4; Cl, 13·7%).

5 : 6 : 7-*Trimethoxyquinoline*. Two attempts to convert 3 : 4 : 5-trimethoxyaniline (Graebe and Suter, *Annalen*, 1905, **340**, 224) into 5 : 6 : 7-trimethoxyquinoline by the Skraup reaction were unsuccessful.

6 : 7-*Methylenedioxyquinoline*, prepared from 3 : 4-methylenedioxyaniline (Rupe and Majewski, *Ber.*, 1900, **33**, 3403) by the Skraup reaction, had b. p. 186—187°/17 mm. and crystallised from light petroleum (b. p. 40—60°) as long needles, m. p. 85° (Found : C, 69·3; H, 4·2; N, 8·05. $C_{10}H_7O_2N$ requires C, 69·4; H, 4·1; N, 8·1%).

8-*Methylthioquinoline*. Quinoline-8-thiol (Edinger, *Ber.*, 1908, **41**, 938) on methylation with methyl iodide and sodium methoxide gave a 70% yield of the crude material, which crystallised from light petroleum (b. p. 40—60°) containing a trace of ether as a cream-coloured powder, m. p. 78—80° (Found : C, 68·1; H, 5·4; N, 7·9; S, 17·8. $C_{10}H_9NS$ requires C, 68·6; H, 5·2; N, 8·0; S, 18·3%).

iso*Quinoline Derivatives*.—1 : 2 : 3 : 4-Tetrahydro-6-methoxy-2-methyl*iso*quinoline gave a picrate as rosettes of needles (from methyl alcohol), m. p. 131—132° (Gulland and Virden, *J.*, 1929, 1798, give 130—131°), and a hydrochloride as prisms (from alcohol–ether), m. p. 170—171° (Buck, *J. Amer. Chem. Soc.*, 1934, **56**, 1771, gives 170°).

6 : 7-*Dimethoxy*isoquinoline. Papaverine was oxidized to papaveraldine by selenium dioxide in 92% yield (Taylor, *J. Pharm. Pharmacol.*, 1950, **2**, 324). This, on fusion with potassium hydroxide (Dobson and Perkin, *J.*, 1911, 136), yielded 6 : 7-dimethoxy*iso*quinoline, b. p. 198—200°/10 mm., m. p. 92° [Dobson and Perkin, *ibid.*, p. 137, give m. p. 94·5°; Forsyth, Kelly, and Pyman, *J.*, 1925, 1666, give 93° (corr.); Spath and Polgar, *Monatsh.*, 1929, **51**, 197, give 93—94°]. Its methiodide, needles (from alcohol), had m. p. 237° (decomp.) (Decker and Koch, *Ber.*, 1905, **38**, 1740, give m. p. 236—237°; Forsyth *et al.*, *loc. cit.*, give m. p. 256°).

1 : 2 : 3 : 4-Tetrahydro-6 : 7-dimethoxy-2-methyl*iso*quinoline, prepared by the reduction of 6 : 7-dimethoxy*iso*quinoline methiodide, crystallised from light petroleum (b. p. 40—60°) as needles, m. p. 82°. The hydrochloride had m. p. 213° and the picrate had m. p. 156—157° (cf. Pyman, *J.*, 1909, 1273; Forsyth, Kelly, and Pyman, *J.*, 1925, 1667; Buck, *J. Amer. Chem. Soc.*, 1934, **56**, 1771).

1 : 2 : 3 : 4-*Tetrahydro*-6 : 7 : 8-*trimethoxy*-2-*methyl*isoquinoline.—N-*Formyl*-2-(3 : 4 : 5-*trimethoxyphenyl*)-*ethylamine* (N-*formylmescaline*). Mescaline (Slotta and Heller, *Ber.*, 1930, **63**, 3040; Slotta and Szyszka, *J. pr. Chem.*, 1933, **137**, 345) (25 g.) and formic acid (17·5 g.; 98—100%) were heated under reflux in an oil-bath at 170° for 5 hours and then cooled. Dry benzene (75 ml.) was added and then distilled off during 45 minutes. The residue was distilled *in vacuo*, and the fraction of b. p. 183—184°/0·2 mm. (27 g.) recrystallised from benzene containing a little light petroleum (b. p. 40—60°), giving N-*formyl*-

TABLE II.

Heterocyclic decamethylenebis(tertiary amines).

Secondary base used.	Properties of bis(tertiary amine). M. p.	B. p.	Cryst. form.	Crystn. solvent.	Found, %. C.	H.	N.	Formula.	Required, %. C.	H.	N.
Piperidine	—	154—156°/0·1 mm.	—	—	77·7	12·7	8·9	$C_{20}H_{40}N_2$	77·9	13·1	9·1
Pyrrolidine	—	146—148°/0·5 mm.	—	—	77·1	13·1	10·0	$C_{18}H_{36}N_2$	77·1	13·0	10·0
1 : 2 : 3 : 4-Tetrahydro*iso*quinoline	57—58°	257—260°/0·5 mm.	Needles	aq. EtOH	82·9	9·9	6·6	$C_{28}H_{40}N_2$	83·2	10·0	6·9
Quinolines.											
1 : 2 : 3 : 4-Tetrahydro-	—	235—240°/0·05 mm.	—	—	83·2	10·0	6·8	$C_{28}H_{40}N_2$	83·2	10·0	6·9
trans-Decahydro-	89—90	238—240°/0·2 mm.	Small clusters	aq. EtOH	80·6	12·5	6·7	$C_{28}H_{52}N_2$	80·8	12·6	6·7
cis-Decahydro-	—	234—236°/0·3 mm.	—	—	80·9	12·6	6·6	$C_{28}H_{52}N_2$	80·8	12·6	6·7
1 : 2 : 3 : 4-Tetrahydro-6-methoxy-	74—75	280—285°/0·2 mm.	Plates	EtOH	77·3	9·35	5·9	$C_{30}H_{44}O_2N_2$	77·6	9·6	6·0
1 : 2 : 3 : 4-Tetrahydro-8-methoxy-	67—69	255—260°/0·1 mm.	Needles	aq. EtOH	77·4	9·35	6·0	$C_{30}H_{44}O_2N_2$	77·6	9·6	6·0
8-Ethoxy-1 : 2 : 3 : 4-tetrahydro-	73—74	262—267°/0·2 mm.	Needles	EtOH	77·8	10·0	5·5	$C_{32}H_{48}O_2N_2$	78·0	9·8	5·7
1 : 2 : 3 : 4-Tetrahydro-6 : 7-dimethoxy-	Not cryst.	Not distilled	—	—	73·6	9·05	5·45	* $C_{32}H_{48}O_4N_2$	73·3	9·2	5·3
,, ,, ,, picrate	144—145 (decomp.)	—	Powder	EtOH	53·3	5·1	11·4	$C_{44}H_{54}O_{18}N_8$	53·8	5·5	11·4

* The analytical figures are of the undistilled material.

TABLE III.

Heterocyclic decamethylenebis(quaternary ammonium salts).

Nature of X in $I^-{}^+\{X\cdot[CH_2]_{10}\cdot X\}^+I^-$	Method.	M. p. (d = decomp.).	Cryst. form.*	Crystn. solvent.	Found, %.† C.	H.	N.	Hal.	Formula.	Required, %. C.	H.	N.	Hal.
Quinolinium	b	213—214° (d)	Yellow	MeOH–EtOH	51·5	5·15	4·4	39·1	$C_{28}H_{34}N_2I_2$	51·5	5·3	4·3	39·0
1 : 2 : 3 : 4-Tetrahydro-1-methylquinolinium	a	152—153 (d)	Cream	EtOH	52·6	6·75	3·7	36·5	$C_{30}H_{46}N_2I_2$	52·3	6·7	4·1	36·9
cis-Decahydro-1-methylquinolinium	a	235—237 (d)	—	EtOH–Et_2O	51·1	8·3	3·8	36·0	$C_{30}H_{58}N_2I_2$	51·4	8·35	4·0	36·3
trans- ,, ,, ,,	a	234—235 (d) [1]	—	EtOH–Et_2O	51·1	8·35	3·9	35·8	$C_{30}H_{58}N_2I_2$	51·4	8·35	4·0	36·3
trans-1-Ethyldecahydroquinolinium	a [2]	238—239 (d)	—	EtOH–Et_2O	52·6	8·45	3·9	35·1	$C_{32}H_{62}N_2I_2$	52·7	8·6	3·85	34·9
6-Methoxyquinolinium	b	185—186 (d)	Yellow plates	MeOH–EtOH	50·4	5·7	3·9	35·1	$C_{30}H_{38}O_2N_2I_2$	50·6	5·4	3·9	35·7
1 : 2 : 3 : 4-Tetrahydro-6-methoxy-1-methylquinolinium	a	168—169	—	EtOH	51·5	6·8	3·75	33·8	$C_{32}H_{50}O_2N_2I_2$	51·3	6·7	3·7	34·0
8-Methoxyquinolinium	b [2]	178—179 (d)	Yellow	EtOH	50·4	5·4	3·7	35·2	$C_{30}H_{38}O_2N_2I_2$	50·6	5·4	3·9	35·7
1 : 2 : 3 : 4-Tetrahydro-8-methoxy-1-methylquinolinium	a [2]	190—191	—	EtOH–Et_2O	51·3	6·9	3·5	34·0	$C_{32}H_{50}O_2N_2I_2$	51·3	6·7	3·7	34·0

Nature of X in $I^-\{X\cdot[CH_2]_{10}\cdot X\}^+I^-$	Method.	M. p. (d = decomp.).	Cryst. form.*	Crystn. solvent.	Found, %.† C.	H.	N.	Hal.	Formula.	Required, %. C.	H.	N.	Hal.
8-Ethoxyquinolinium	b [2]	182—183 (d)	Yellow plates	EtOH	51·6	6·1	3·9	34·7	$C_{32}H_{42}O_2N_2I_2$	51·9	5·7	3·8	34·3
8-Ethoxy-1 : 2 : 3 : 4-tetrahydro-1-methylquinolinium	a	177—178	—	EtOH–Et_2O	52·3	7·15	3·6	32·5	$C_{34}H_{54}O_2N_2I_2$	52·6	7·0	3·6	32·7
6 : 7-Dimethoxyquinolinium	b	207—209 (d)	Yellow	MeOH–EtOH	49·5	5·5	3·5	32·8	$C_{32}H_{42}O_4N_2I_2$	49·7	5·5	3·6	32·9
1 : 2 : 3 : 4-Tetrahydro-6 : 7-dimethoxy-1-methylquinolinium	a	209—211	Nodules	EtOH	50·4	6·9	3·5	31·2	$C_{34}H_{54}O_4N_2I_2$	50·5	6·7	3·5	31·4
*iso*Quinolinium [4]	b	Sinters at 135—136°, melts at 171° (d)	Felted mass of small cream needles	EtOH	60·4	6·0	4·8	28·7	$C_{28}H_{34}N_2Br_2$	60·2	6·1	5·0	28·7
*iso*Quinolinium	b	194	Lemon-yellow needles	EtOH	51·5	5·4	4·2	38·6	$C_{28}H_{34}N_2I_2$	51·5	5·3	4·3	39·0
1 : 2 : 3 : 4-Tetrahydro-2-methyl*iso*quinolinium	a	225	—	MeOH–EtOH	52·1	6·5	4·0	37·0	$C_{30}H_{46}N_2I_2$	52·3	6·7	4·1	36·9
cis-Decahydro-2-methyl*iso*quinolinium	b	201—202	—	EtOH	51·2	8·3	3·85	36·2	$C_{30}H_{58}N_2I_2$	51·4	8·35	4·0	36·3
1 : 2 : 3 : 4-Tetrahydro-6-methoxy-2-methyl*iso*quinolinium	b	182—184	—	EtOH	51·2	6·8	3·55	34·1	$C_{32}H_{50}O_2N_2I_2$	51·3	6·7	3·7	34·0
6 : 7-Dimethoxy*iso*quinolinium	b	208—210 (d)	Pale yellow needles	MeOH–EtOH	49·2	5·3	3·7	32·7	$C_{32}H_{42}O_4N_2I_2$	49·7	5·5	3·6	32·9
1 : 2 : 3 : 4-Tetrahydro-6 : 7-dimethoxy-2-methyl*iso*quinolinium	b	226—228 (d)	Cream	MeOH–EtOH	50·2	6·75	3·3	31·4	$C_{34}H_{54}O_4N_2I_2$	50·5	6·7	3·5	31·4
1 : 2 : 3 : 4-Tetrahydro-6 : 7 : 8-trimethoxy-2-methyl*iso*quinolinium	b	188—190 (d)	Cream nodules	MeOH–EtOH	49·7	6·7	3·0	29·3	$C_{36}H_{58}O_6N_2I_2$	49·8	6·7	3·2	29·3
1: 2 : 3 : 4-Tetrahydro-2-methyl-6 : 7-methylenedioxy*iso*quinolinium	b	222—224	—	MeOH–EtOH	49·6	6·0	3·5	32·6	$C_{32}H_{46}O_4N_2I_2$	49·5	6·0	3·6	32·7
1 : 2 : 3 : 4-Tetrahydro-8-methoxy-2-methyl-6 : 7-methylenedioxy*iso*quinolinium	b	225—227 (d)	—	MeOH–EtOH	48·7	6·0	3·2	30·5	$C_{34}H_{50}O_6N_2I_2$	48·8	6·0	3·35	30·4
1-Methylpiperidinium	a	248 (d)	Needles	EtOH	44·6	7·7	4·7	42·4	$C_{22}H_{46}N_2I_2$	44·6	7·8	4·7	42·9
3-Bromopyridinium	b	173—174	Pale yellow needles [5]	MeOH–EtOH	34·2	4·0	4·05	57·8	$C_{20}H_{28}N_2Br_2I_2$	33·8	4·0	3·9	58·3
3-Methoxypyridinium	b	103—105	Very pale yellow	EtOH	43·3	5·7	4·4	41·1	$C_{22}H_{34}O_2N_2I_2$	43·1	5·6	4·6	41·5
1-Methylpyrrolidinium	a	246—247	Needles	EtOH	42·4	7·5	4·9	45·1	$C_{20}H_{42}N_2I_2$	42·6	7·5	5·0	45·0

* Microcrystalline and colourless unless otherwise stated. † Dried at 100° *in vacuo*.

[1] Mixed m. p. with *cis*-derivative, 218—222°. [2] Reaction slow. [3] Reaction very slow—necessary to use alcohol as solvent instead of benzene. [4] Bromide. Crystals contain $2H_2O$ of crystn. (Hartwell and Pogorelskin, *J. Amer. Chem. Soc.*, 1950, **72**, 2043, give m. p. range of the dihydrate " 136 to 180°, giving off vapour at 144—162° "; Barlow and Ing., *Brit. J. Pharmacol.*, 1948, **3**, 298, give m. p. 113°). [5] Crystals contain $2H_2O$ of crystn.

In general, those compounds in which the quaternary nitrogen is present in a reduced ring are colourless or cream-coloured. When the quaternary nitrogen is situated in an unsaturated ring, the resulting iodides are generally yellow or orange, although the bromides are colourless or cream coloured.

mescaline (23 g.) as needles, m. p. 68—69° (Found: C, 60·1; H, 6·95; N, 5·65. $C_{12}H_{17}O_4N$ requires C, 60·25; H, 7·2; N, 5·9%).

3 : 4-*Dihydro*-6 : 7 : 8-*trimethoxy*isoquinoline. *N*-Formylmescaline (23 g.), in a 250-ml. flask fitted with a reflux condenser, was cooled in ice, and phosphorus oxychloride (40 ml.) added through the condenser. When the initial vigorous reaction had subsided, the red solution was heated under reflux on the steam-bath for 90 minutes. After cooling, it was poured into light petroleum (b. p. 40—60°), with stirring, the petroleum decanted off, and the lower layer washed three times by decantation with light petroleum. It was then dissolved in dilute hydrochloric acid, the solution washed once with benzene, made alkaline with sodium hydroxide, and the resulting oil extracted with benzene. The benzene solution was shaken with solid potassium hydroxide and filtered, the benzene recovered, and the residue distilled *in vacuo*. The fraction of b. p. 138—140°/0·5 mm. (16·5 g.) was recrystallised from benzene–light petroleum (b. p. 40—60°). The *product* (15 g.) separated as rhombs, m. p. 91—92° (Found: C, 64·8; H, 6·9; N, 6·2. $C_{12}H_{15}O_3N$ requires C, 65·2; H, 6·8; N, 6·3%).

Its *methiodide*, fine pale yellow needles (from methyl alcohol), had m. p. 179—180° (decomp.) (Found: C, 43·2; H, 4·9; N, 3·8; I, 34·7. $C_{13}H_{18}O_3NI$ requires C, 43·0; H, 5·0; N, 3·9; I, 35·0%). Its *ethiodide*, fine pale yellow needles (from alcohol–ether), had m. p. 155—157° (decomp.) (Found: C, 44·7; H, 5·3; N, 3·8; I, 33·4. $C_{14}H_{20}O_3NI$ requires C, 44·6; H, 5·35; N, 3·7; I, 33·7%).

1 : 2 : 3 : 4-*Tetrahydro*-6 : 7 : 8-*trimethoxy*-2-*methyl*isoquinoline was prepared by reduction of the above methiodide (19 g.) by hydrochloric acid (240 ml. of concentrated acid in 240 ml. of water) and excess of zinc dust. After being made alkaline with excess of ammonia, the cooled solution was extracted with ether in a continuous-extraction apparatus, the ethereal extract dried (Na_2SO_4), the solvent recovered, and the residue distilled *in vacuo*. The *product* (10·5 g.) had b. p. 122—124°/0·5 mm. (Found: C, 65·8; H, 8·0; N, 5·8. $C_{13}H_{19}O_3N$ requires C, 65·8; H, 8·1; N, 5·9%). The *picrate*, thick needles (from alcohol), had m. p. 135° (Found: C, 48·9; H, 4·75; N, 11·6. $C_{19}H_{22}O_{10}N_4$ requires C, 48·9; H, 4·8; N, 12·0%).

2-*Ethyl*-1 : 2 : 3 : 4-*tetrahydro*-6 : 7 : 8-*trimethoxy*isoquinoline (1·25 g.), obtained by reduction of 3 : 4-dihydro-6 : 7 : 8-trimethoxy*iso*quinoline ethiodide (4·75 g.), had b. p. 107—109/0·05 mm. (Found: C, 66·5; H, 8·6; N, 5·8. $C_{14}H_{21}O_3N$ requires C, 66·9; H, 8·4; N, 5·6%). Its *methiodide*, colourless prisms (from alcohol), had m. p. 171—172° (decomp.) (Found: C, 45·9; H, 5·85; N, 3·45; I, 32·1. $C_{15}H_{24}O_3NI$ requires C, 45·8; H, 6·2; N, 3·6; I, 32·3%).

6 : 7 : 8-*Triethoxy*-1 : 2 : 3 : 4-*tetrahydro*-2-*methyl*isoquinoline was prepared from 2-(3 : 4 : 5-triethoxyphenyl)ethylamine (14 g.) (Slotta and Szyszka, *loc. cit.*, p. 349) in a manner analogous to the preparation of the corresponding trimethoxy-compound from mescaline, *via* the following intermediates: *N-formyl*-2-(3 : 4 : 5-*triethoxyphenyl*)*ethylamine* (12 g.), leaflets [from benzene–light petroleum (b. p. 40—60°)], m. p. 67—69°, b. p. 178—180°/0·1 mm. (Found: C, 64·0; H, 8·2; N, 5·0. $C_{15}H_{23}O_4N$ requires C, 64·1; H, 8·25; N, 5·0%); 6 : 7 : 8-*triethoxy*-3 : 4-*dihydro*isoquinoline (9 g.), needles [from light petroleum (b. p. 40—60°)], m. p. 44—46°, b. p. 120—122°/0·1 mm. (Found: C, 68·5; H, 8·0; N, 5·35. $C_{15}H_{21}O_3N$ requires C, 68·4; H, 8·05; N, 5·3%) [*methiodide* (12 g.), pale yellow needles (from alcohol), m. p. 203° (decomp.) (Found: C, 47·2; H, 5·85; N, 3·4; I, 31·5. $C_{16}H_{24}O_3NI$ requires C, 47·4; H, 6·0; N, 3·5; I, 31·4%)]; 6 : 7 : 8-*triethoxy*-1 : 2 : 3 : 4-*tetrahydro*-2-*methyl*isoquinoline, (7 g.), b. p. 127—129°/0·2 mm. (Found: C, 68·5; H, 9·2; N, 4·9. $C_{16}H_{25}O_3N$ requires C, 68·8; H, 9·0; N, 5·0%) [*methiodide*, colourless glistening plates (from alcohol), m. p. 215—216° (Found: C, 48·5; H, 6·7; N, 3·2; I, 30·4. $C_{17}H_{28}O_3NI$ requires C, 48·5; H, 6·7; N, 3·3; I, 30·2%)].

1 : 2 : 3 : 4-Tetrahydro-2-methyl-6 : 7-methylenedioxy*iso*quinoline (hydrohydrastinine), prepared by reduction of 3 : 4-dihydro-6 : 7-methylenedioxy*iso*quinoline methiodide (Spath and Polgar, *Monatsh.*, 1929, **51**, 201; Decker, *Annalen*, 1913, **395**, 324), needles [from light petroleum (b. p. 40—60°)], had m. p. 61° (Fritsch, *Annalen*, 1895, **286**, 18, gives m. p. 60—61°; Freund and Will, *Ber.*, 1877, **20**, 93, give m. p. 66°; Clayson, *J.*, 1949, 2018, gives m. p. 61°).

Pyridine Derivatives.—2-Methoxypyridine, prepared by treatment of the silver derivative of α-pyridone with methyl iodide, had b. p. 144—145° (von Pechmann and Baltzer, *Ber.*, 1891, **24**, 3149, prepared this substance, but did not quote the b. p.) (Found: C, 65·7; H, 6·8; N, 12·7. Calc. for C_6H_7ON: C, 66·1; H, 6·5; N, 12·8%).

3-Methoxypyridine, prepared in a similar manner, had b. p. 182° (Koenigs, Gerdes, and Sirot, *Ber.*, 1928, **61**, 1022, give b. p. 179°).

II. *Preparation of Heterocyclic Decamethylenebis*(*tertiary Amines*).—These were prepared by refluxing a decamethylene dihalide with an excess of the appropriate heterocyclic secondary amine in benzene. One example is given in detail; the properties of the other bis(tertiary amines) are listed in Table II.

1 : 10-*Dimorpholino*-n-*decane*. Decamethylene dibromide (15 g.) and morpholine (26 g., 6 mols.) in dry benzene (45 ml.) were refluxed on the steam-bath for 24 hours. There was an almost immediate precipitate of morpholine hydrobromide. The mixture was then poured into a slight excess of dilute hydrochloric acid. The benzene layer was separated, washed once with dilute hydrochloric acid, and discarded. The combined aqueous layers were washed with benzene and made alkaline with sodium hydroxide, the resulting oil was extracted with ether, and the ethereal extract washed with water, and dried (Na_2SO_4). After filtration and recovery of the solvent, the residue was distilled *in vacuo*. The fraction, b. p. 162—164°/0·01 mm. (14 g.), of 1 : 10-*dimorpholino*-n-*decane* crystallised in needles, m. p. 48°. Recrystallisation from aqueous alcohol did not alter the m. p. (Found: C, 69·1; H, 11·3; N, 9·0. $C_{18}H_{36}O_2N_2$ requires C, 69·2; H, 11·6; N, 9·0%). The hydrochloride of this base has been described by Goodson *et al.* (*Brit. J. Pharmacol.*, 1948, **3**, 60) as needles, m. p. 240—242°.

III. *Preparation of Heterocyclic Decamethylenebis*(*quaternary Ammonium*) *Salts*.—These were obtained by two general methods:

(*a*) By the action of an alkyl halide on an ethereal or benzene solution of a heterocyclic decamethylenebis(tertiary amine), for example : *Decamethylenebis(morpholinium methiodide)*. 1 : 10-Dimorpholino-*n*-decane (10·4 g.) in dry ether (25 ml.) was treated with methyl iodide (14 g., 50% excess) in dry ether (25 ml.). The mixture soon deposited crystals. After 2 days at room temperature, the mixture became almost solid. It was filtered, and the solid washed thoroughly with dry ether, and recrystallised from anhydrous alcohol, giving *decamethylenebis(morpholinium methiodide)* (15 g.) as colourless needles, m. p. 217—218° (decomp.) (Found : C, 40·2; H, 7·05; N, 4·6; I, 42·7. $C_{20}H_{42}O_2N_2I_2$ requires C, 40·3; H, 7·1; N, 4·7; I, 42·6%).

(*b*) By refluxing an excess of the appropriate heterocyclic tertiary amine with a decamethylene dihalide in a neutral solvent, for example : *Decamethylenebis(pyridinium bromide)*. Decamethylene dibromide (10 g.) pyridine (8 g., 3 mols.) in dry benzene (40 ml.) were heated under reflux on the steam-bath for 24 hours. The solution deposited crystals within 15 minutes. After cooling and filtration, the precipitate was washed with dry benzene and recrystallised from anhydrous alcohol, giving *decamethylenebis(pyridinium bromide)* (12 g.) as small hard colourless rhombs, m. p. 194—195 (Found : C, 52·6; H, 6·7; N, 6·0; Br, 34·7. Calc. for $C_{20}H_{30}N_2Br_2$: C, 52·4; H, 6·6; N, 6·1; Br, 34·9%) (Hartwell and Pogorelskin, *J. Amer. Chem. Soc.*, 1950, **72**, 2041, give m. p. 196·5—198°).

The properties of the remaining bis(quaternary ammonium salts) are listed in Table III, the notation (a) or (b) indicating the method of preparation.

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